features observed in peripheral blood, or serum immunoglobulin levels (IgM peak 12.7 g/l). After this period, she ceased smoking and a reduction in the percentage of lymphocytes in peripheral blood was observed (mean 48%), though the abnormal forms persisted (1%). In the same way a reduction in the level of serum IgM was observed (mean 4.85 g/l). HLA-typing performed later showed that our patient was negative for HLA-DR7. A study of her relatives (parents and sister) failed to disclose similar abnormalities (binucleated lymphocytes or increased IgM).

Since this syndrome was first described by Gordon et al. [1], several possible etiologic mechanisms have been suggested, including: (a) genetic predisposition [2–4], based on HLA-DR7 positivity in most patients and the presence of binucleated lymphocytes in their relatives, though the complete syndrome may be absent; (b) cigarette smoking [4,5]: a great number of these females were smokers, and in a patient reported by Carstairs et al. [5] a cure of the lymphocytosis was observed when she stopped smoking; and (c) viral infection: Chow et al. [6] demonstrated EBV DNA in lymphocytes of two patients suffering from this syndrome. In our case, the patient was HLA-DR7-negative and none of her relatives presented with similar abnormalities in peripheral blood, making the genetic hypothesis improbable. Marked reductions in serum IgM levels, in the absolute number of lymphocytes, and in the percentage of binucleated forms were observed when the patient stopped smoking. Finally, the hypothesis of EBV as the cause of this syndrome cannot be excluded since a prior infection has been demonstrated in the patient. In our opinion, this polyclonal B-cell lymphocytosis is a disorder which should be grouped with several others with differing clinical expressions. Some patients have presented with splenomegaly or adenopathies [1–4], which have still to be clearly defined.

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Thrombin–Antithrombin III and Prothrombin Fragment 1.2 Levels in Early Respiratory Distress Syndrome

To the Editor: Disseminated intravascular coagulation (DIC) is frequently encountered in preterm neonates with advanced respiratory distress syndrome (RDS) [1]. However, we previously reported normal plasma fibrinogen, antithrombin III (AT-III), protein C, and tissue plasminogen activator but lower D-dimer and higher plasminogen activator inhibitor (PAI) levels within the first few hours of life in preterm infants who later developed RDS compared to control group [2]. These changes in D-dimer and PAI levels are probably related to abnormalities in the fibrinolytic mechanism due to lung damage and local platelet activation in RDS. Therefore, we studied some of the more specific DIC parameters in these patients to evaluate the coagulation disorders in detail.

TABLE I. TAT and F1.2 Levels in Preterm Infants With or Without RDS (Mean ± SD)

	Controls (n = 20)	Infants with RDS (n = 15)
Gestational age (weeks)	32.1 ± 2.1	32.4 ± 1.7
Birth weight (g)	1614 ± 439	1851 ± 602
TAT (μg/l)	78.12 ± 72.75	64.83 ± 69.91
F1.2 (nmol/l)	9.02 ± 7.37	9.87 ± 5.67

Abbreviations: TAT, thrombin/antithrombin III complex, F1.2, prothrombin fragment 1.2; RDS, respiratory distress syndrome.

Theoretically, the specific detection of thrombin should be suitable for use in the active state of DIC. However, thrombin is very rapidly bound and thereby inactivated by its main physiological inhibitor, AT-III. For this reason, a more direct method to evaluate the thrombin level is to measure the thrombin/antithrombin III complex (TAT) formed with AT-III. Patients with DIC are found to have elevated concentrations of TAT [3–6]. In practice, thrombin can, therefore, be measured only indirectly, by assaying the cleavage products of prothrombin released during the conversion to thrombin (prothrombin fragment 1.2 [F1.2]) or by assaying activation products of substrates of thrombin (fibrinogen, fibrin degradation products, fibrinopeptidase A, etc.). The assays commonly used—i.e., prothrombin time, activated partial thromboplastin time, fibrinogen or fibrin degredation products—are insensitive and nonspecific in the diagnosis of DIC [7]. However, F1.2 is a polypeptide released from prothrombin during its activation to thrombin. F1.2 is a biological marker of the thrombin generation, and it has been demonstrated to correlate with the thrombotic risk associated with certain patient populations [8–10].

Therefore, we studied serum TAT and F1.2 status in 35 preterm infants with or without RDS in the first few hours of life. All neonates received vitamin K1, 1 mg, intramuscularly upon delivery. Blood samples for TAT (enzyme immunoassay method; Enzygost TAT micro, Behring, Germany) [6] and F1.2 (sandwich-type ELISA method; Enzygnost F 1 + 2 micro, Behring) [10] testing were obtained from a peripheral vein within 6 hr after birth and mixed with 3.8% trisodium citrate according to their hematocrit levels. The tubes were centrifuged at about 3,000 rpm for 10 min within 30 min of collection. The plasma was stored at −20°C less than 1 month before the procedure.

Among 35 infants, 20 who were in stable clinical condition served as the control group. Fifteen developed RDS, which was considered to be present if all of the following diagnostic criteria were fullfilled: symptoms of respiratory distress within 1 hr after birth and present for at least 24 hr, respiratory support including mechanical ventilation, and typical findings on lung x-ray and arterial blood gas analysis. None of the infants with RDS had any other disease. The mean plasma TAT and F1.2 levels were found to be similar in the two groups ($P > 0.05$ by Mann-Whitney U test; Table I).

These relatively more specific parameters (i.e., TAT and F1.2) of DIC support our previous hypothesis, as DIC is not a prominent event in early (or developing) RDS [2]. For this reason, further studies are needed to show the other abnormalities in the hemostatic system and their pathogenic significance in RDS. The main limitation in these studies is the ethical dilemma of attaining enough blood samples in the first few hours of life to evaluate the various parameters of coagulation and the fibrinolytic system simultaneously. The accumulated findings from different centers in the literature will be useful in reaching a reliable conclusion.

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Treatment and Prophylaxis of Hypermenorrhea With Leuprorelin in Premenopausal Women Affected by Acute Leukemia at Diagnosis

To the Editor: Women affected by acute leukemia (AL) often show hypermenorrhea at diagnosis or after chemotherapy [1], increasing supportive care and transfusional needs and influencing performance status. The effect of leuprorelin, a Gn-rh analogue which induces profound amenorrhea, in premenopausal AL women showing vaginal bleeding at diagnosis is reported. Sixteen premenopausal women with AL were treated with standard chemotherapy, including antracyclines. Characteristics of patients are shown in Table I. Eight of them received oral contraceptives (OC) (gestodene, 0.075 mg, and ethynil estradiol, 0.03 mg, daily; group A) until resolution of thrombocytopenia or when toxicity occurred (median days 17.5). When leuprorelin (Enantone Depot, Takeda, Osaka, Japan) became commercially available, it was administered, after informed consent, to eight patients (3.75 mg/q 28 days sc) in combination with OC (median days 16) to prevent leuprorelin "flare-up" (group B).

Results were expressed as median values. Probability of significant differences between groups was assessed by Mann-Whitney U test for unpaired groups and $\times 2$ test on 2×2 tables. Statistical significance was $P = 0.05$.

Results are summarized in Table 1. Vaginal bleeding lasted a median of 3 and 5 days in groups A and B (P = NS), respectively. There was no statistically significant difference in supportive measures (median values: group A 7 red blood cell units [RBCu] and 5.5 single donor platelet units [SDPu]; group B 10 RBCu and 9.5 SDPu).

Liver toxicity grade I–II was observed in two of eight patients in group A and in five of seven in group B; three of eight patients in group A developed grade III–IV toxicity (P = NS). OC discontinuation was necessary in three of eight patients in group A and in five of seven patients in group B with resolution of liver damage. Three patients in group A discontinued OC for concomitant therapy with L-asparaginase. No side effects attributable to leuprorelin were encountered in group B. Upon OC withdrawal, vaginal bleeding occurred in six of eight patients in group A; no patient in group B developed vaginal bleeding ($P = 0.009$).

In premenopausal leukemic patients, significant blood losses may derive from uncontrolled vaginal bleeding, which per se determines an important discomfort and may increase susceptibility to infections due to lack of mucosal integrity [2]. The use of OC, despite a rapid control of vaginal bleeding, may adversely affect liver function [3], potentiating toxicity related to chemotherapy or antibacterial or antifungal agents; OC may affect the hemostatic system, inducing a prothrombotic effect [4] amplified by the use of specific antitumor drugs like L-asparaginase [5]. The compliance of oral administration is poor. Our data confirm that early discontinuation of OC may be necessary. Leuprorelin determines a profound amenorrhea acting on the hypothalamic–gonadal axis, but its effect is not as rapid as that of OC. The temporary agonist effect requires OC in combination early during thrombocytopenia. Our experience showed the feasibility and efficacy of leuprorelin. Compliance was optimal and safety profile good. No statistical differences were observed in the two groups in terms of toxicity, likely related to the contemporary use of OC or in length of vaginal bleeding and transfusional support. A significant difference occurred in resumption of vaginal bleeding upon OC discontinuation, reflecting the different biological mechanism of amenorrhea induced by leuprorelin, which is profound and long-lasting. Further reduction of liver toxicity

TABLE I. Characteristics of Patients

	Group A	Group B	*P*
Age (years)	29.5 (13–43)	39 (26–41)	0.042
Diagnosis	AML 5; ALL 3	AML 7; ALL 1	0.56
Platelet count × 10e9/l	27.5 (7–49)	28 (12–83)	0.3
Vaginal bleeding	6/8	7/8	1
Length of VB	3 (1–26)	5 (2–34)	0.28
RBCu	7 (2–21)	10 (3–15)	0.35
SDPu	5.5 (1–15)	11 (1–16)	0.35
Liver toxicity	5/8	5/8	1
WHO grade I–II	2/8	5/8	NS
WHO grade III–IV	3/8	0/8	0.20
Bleeding resumption	6/8	0/8	0.009
Days to platelets >50 × 10e9/l	17 (6–25)	21 (6–34)	0.23

VB, vaginal bleeding; RBCu, red blood cell units; SDPu, single donor platelet units. Age, platelet count, length of VB, RBCu, PLTsu, and days to platelets >50 × 10e9/l are expressed as median values.